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(71) Applicant: **ELI LILLY AND COMPANY**  
**Indianapolis, Indiana 46285 (US)**

(72) Inventors:  
• **Oguiza, Juan Ignacio**  
**28700 San Sebastian de los Reyes Madrid (ES)**

• **Wong, David Taiwai**  
**Indianapolis, Indiana 46226 (US)**

(74) Representative: **Tapping, Kenneth George et al**  
**Lilly Industries Limited**  
**European Patent Operations**  
**Erl Wood Manor**  
**Windlesham Surrey GU20 6PH (GB)**

(54) **Potentiation of drug response by a serotonin 1A receptor antagonist**

(57) The power of citalopram, fluvoxamine and paroxetine to increase the availability of serotonin, nore-

pinephrine and dopamine, particularly serotonin, is augmented by administration in combination with a drug which is a serotonin 1A receptor antagonist.

**EP 0 714 663 A2**

## Description

The present invention belongs to the fields of pharmacology, medicine and medicinal chemistry, and provides a method and compositions for increasing the availability of serotonin, norepinephrine and dopamine in the brain of patients to whom is administered citalopram, fluvoxamine or paroxetine.

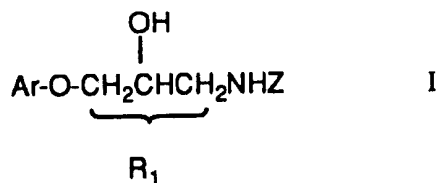
Over the past twenty years or more, the science of pharmacology has been particularly interested in the physiology of the neurons containing monoamines in the human brain. Discovery has followed discovery in the field and it has now been demonstrated that serotonin, norepinephrine and dopamine interact with a great number of receptors in the brain and control or affect processes which regulate many bodily organs and functions. Serotonin, particularly, has been found to be the key to a large number of processes which reveal themselves in both physiological and psychological functions.

Perhaps the most dramatic discovery in medicinal chemistry in the recent past are the serotonin reuptake inhibitors, which are extremely effective in the treatment of depression. They increase the availability of serotonin in the synapse by reducing the uptake of serotonin by the serotonin uptake carrier. Dysfunction of the serotonin neurons resulting from excessive uptake results in depression, as well as other pathologies of the central nervous system. Not only are these drugs spectacularly effective in depression, they are also effective in treating numerous other conditions.

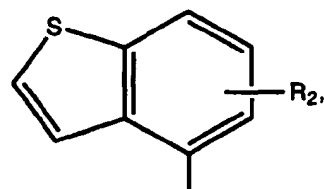
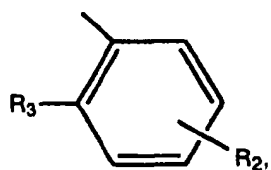
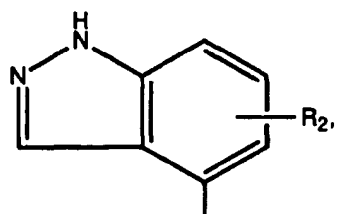
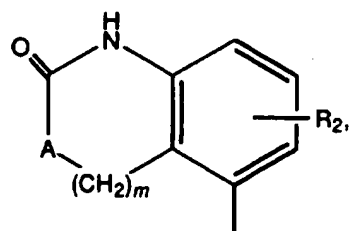
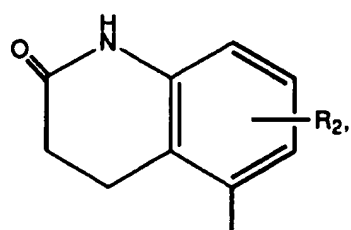
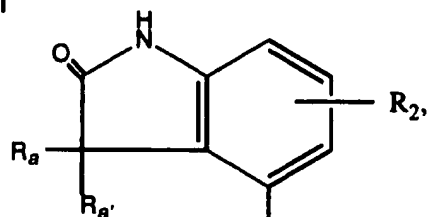
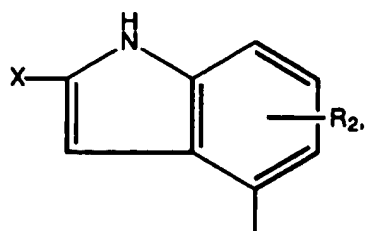
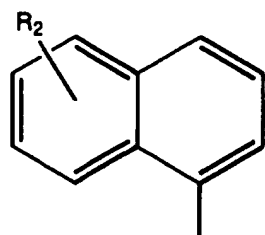
Among the serotonin reuptake inhibitors are citalopram, fluvoxamine and paroxetine. While the primary activity of these drugs is the inhibition of the reuptake of serotonin, the cascade of monoamine processes in the brain connects serotonin with both norepinephrine and dopamine. Thus, the increase of availability of serotonin results in increased availability of norepinephrine and dopamine as well.

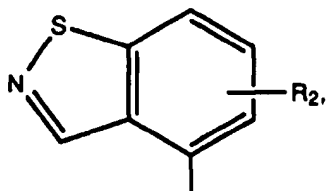
The present invention provides a method for increasing the availability of serotonin, norepinephrine and dopamine, even compared to the usual increased availability caused by citalopram, fluvoxamine and paroxetine, by potentiating the action of those drugs.

The invention provides a method for potentiating the action of a first component chosen from the group consisting of citalopram, fluvoxamine and paroxetine in increasing the availability of serotonin, norepinephrine and dopamine in the brain, comprising administering a first component in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula

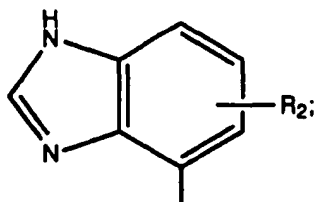


wherein Ar is

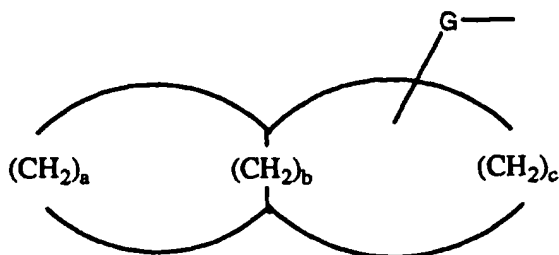




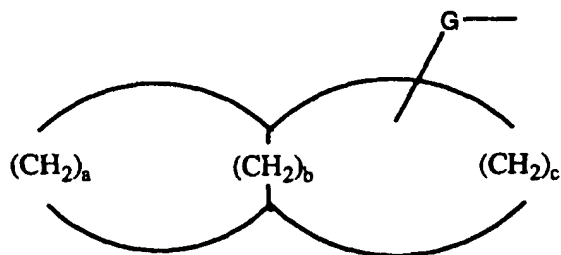
or



$R_1$  is an optional methyl group substituted on one of the three connecting carbon atoms;  
 $R_2$  is hydrogen,  $C_1$ - $C_4$  alkyl, trifluoromethyl, hydroxy,  $(C_1$ - $C_4$  alkyl)-O-,  $(C_1$ - $C_4$  alkyl)-S(O) $_p$ -, or halo;  
 $R_3$  is  $C_3$ - $C_8$  cycloalkyl or a bicycloalkyl group of the formula



where  $a$  and  $c$  are independently 1-5,  $b$  is 0-5, and  $(a+c)$  is greater than 2;  
 $Z$  is a straight or branched  $C_4$ - $C_{10}$  alkane, alkene, or alkyne group;  $(C_4$ - $C_8$  cycloalkyl) optionally substituted with  $C_1$ - $C_4$  alkyl or phenyl; a bicycloalkyl group of the formula



wherein  $a$  and  $c$  are independently 1-5,  $b$  is 0-5, and  $(a+c)$  is greater than 2; optionally phenyl substituted  $C_2$ - $C_{10}$  alkyl where the phenyl group can be optionally substituted with  $R_2$  as previously defined; or  $(C_1$ - $C_4$  alkylidene)-T- $(C_1$ - $C_4$  alkyl), where T is -O-, -S-, -SO-, or -SO $_2$ -;

where

each G is independently a bond or  $C_1$ - $C_4$  alkylidene;

X is -H, -COY, -CN, or  $C_1$ - $C_4$  alkyl;

Y is -OH, -O- $(C_1$ - $C_4$  alkyl), or -NH $_2$ ;

$R_a$  and  $R_a'$  are independently hydrogen or  $C_1$ - $C_3$  alkyl, or when taken together with the carbon atom to which they are attached form a  $C_3$ - $C_8$  cycloalkyl ring;

$p$  is 0, 1, or 2;

A is -O-, -S-, -NH-, or -NCH<sub>3</sub>-; and

m is 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof;

provided that when the first component is citalopram, the second component is not (S)-UH-301 or penbutolol; and

provided that when the first component is paroxetine or fluvoxamine, the second component is not pindolol.

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The invention also provides pharmaceutical compositions which comprise a first component in combination with one of the second component compounds named above. Further, it provides methods of treating a pathological condition which is created by or is dependent upon decreased availability of serotonin, dopamine or norepinephrine, which comprise administering to a patient in need of such treatment an adjunctive therapy comprising a first component and one of the compounds named above.

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The invention also provides the use of the above combination of drugs for potentiating the action of a first component compound, and the use of the above combination for manufacturing a medicament for the same purpose. Additionally, it provides the use of the combination for treating pathological conditions created by or dependent upon decreased availability of serotonin, norepinephrine or dopamine, and for manufacture of a medicament for such purpose.

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Still further, the invention provides a preferred manner of carrying out the above method of adjunctive therapy, wherein the provisos above are disregarded, wherein the second component is administered in a manner which provides a substantially constant blood level of the second component, which level is sufficient to provide a substantially constant degree of potentiation of the action of the first component. Compositions adapted for carrying out the preferred manner of the invention are also provided.

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In this document, all temperatures are described in degrees Celsius, and all amounts, ratios of amounts and concentrations are described in weight units unless otherwise stated.

### The Compounds

25

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in U.S. Patent 4,136,193 as a serotonin reuptake inhibitor. Its pharmacology was disclosed by Christensen *et al.*, *Eur. J. Pharmacol.* **41**, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour *et al.*, *Int. Clin. Psychopharmacol.* **2**, 225 (1987), and Timmerman *et al.*, *ibid.*, 239.

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Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone O-(2-aminoethyl)oxime, is taught by U.S. Patent 4,085,225. Scientific articles about the drug have been published by Claassen *et al.*, *Brit. J. Pharmacol.* **60**, 505 (1977); and De Wilde *et al.*, *J. Affective Disord.* **4**, 249 (1982); and Benfield *et al.*, *Drugs* **32**, 313 (1986).

35

Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Patents 3,912,743 and 4,007,196. Reports of the drug's activity are in Lassen, *Eur. J. Pharmacol.* **47**, 351 (1978); Hassan *et al.*, *Brit. J. Clin. Pharmacol.* **19**, 705 (1985); Laursen *et al.*, *Acta Psychiat. Scand.* **71**, 249 (1985); and Battagay *et al.*, *Neuropsychobiology* **13**, 31 (1985).

The first components are known to increase the availability of serotonin (5-HT), dopamine (DA) and norepinephrine (NE), and the second component drugs potentiate that valuable property. The second component drugs have in common the property of being antagonists of the serotonin 1A receptor.

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(S)-UH-301 ((S)-5-fluoro-8-hydroxy-2-dipropylaminotetralin) is well known to pharmacologists and pharmaceutical chemists. Hillver *et al.* taught its synthesis in *J. Med. Chem.* **33**, 1541-44 (1990) and Moreau *et al.*, *Brain Res. Bull.* **29**, 901-04 (1992) provided considerable in vivo data about the compound.

Alprenolol (1-(1-methylethyl)amino-3-[2-(2-propenyl)phenoxy]-2-propanol) was disclosed by Brandstrom *et al.*, U.S. Patent 3,466,325, which shows its preparation as Example 5.

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WAY 100135 (N-(t-butyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide) was disclosed by Abou-Gharbia *et al.*, U.S. Patent 4,988,814, who taught that the compound has affinity for the 5-HT<sub>1A</sub> receptor. Cliffe *et al.*, *J. Med. Chem.* **36**, 1509-10 (1993) showed that the compound is a 5-HT<sub>1A</sub> antagonist.

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WAY 100635 (N-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide) was put in the literature by Cliffe *et al.*, European Patent Publication 0512755, published November 11, 1992. A number of papers about the compound and its activity as a 5-HT<sub>1A</sub> antagonist were presented at the IUPHAR Satellite Meeting on Serotonin, July 30, 1994, Chicago, IL, and abstracts were published.

Spiperone (8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one) is a well-known compound, taught in U.S. Patents 3,155,669 and 3,155,670. Its activity as a 5-HT<sub>1A</sub> antagonist is shown by Middlemiss *et al.*, *Neurosci. and Biobehav. Rev.* **16**, 75-82 (1992).

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Tertatolol (8-(3-t-butylamino-2-hydroxypropyloxy)thiochroman) was disclosed by Malen *et al.*, U.S. Patent 3,960,891, which teaches it to be a blocker of cardiac beta-adrenergic receptors. Its other activities, including the presently used 5-HT<sub>1A</sub> antagonist activity, have been discovered since the original patents appeared.

Propranolol (1-isopropylamino-3-(1-naphthalenyloxy)-2-propanol) was disclosed by Crowther *et al.*, U.S. Patent 3,337,628 to be a beta-blocker like tertatolol. Again, its other properties are also well known to pharmacologists.

Penbutolol (1-(t-butylamino)-2-hydroxy-3-(2-cyclopentyl-phenoxy)propane) was taught by Ruschig *et al.*, U.S. Patent 3,551,493, which describes it as a beta-blocker. Both the (-) and the (+) enantiomers of penbutolol are of interest; the (-) enantiomer is preferred for the present purpose but both enantiomers and the racemic mixture are included in the word "penbutolol" in this document.

Pindolol (4-(2-hydroxy-3-isopropylaminopropoxy)indole) was disclosed by Troxler *et al.*, U.S. Patent 3,471,515, which describes this compound as well as a beta-blocker. The compound is usually administered as the racemic mixture, but the two enantiomers have been isolated and the (-) enantiomer is preferred if a single isomer product is desired in a given application. Both enantiomers and the racemic mixture are included in the word "pindolol" in this document.

The compounds of formula I are taught by Beedle, *et al.*, U.S. patent 5,013,761, the description of which is incorporated herein by reference. The synthesis and characteristics, including the 5HT<sub>1A</sub> antagonist activity, of the compounds is shown in that patent.

The particularly preferred compounds of formula I include, for example, the following individual compounds. It will be understood that the following compounds are typical of those of formula 1 but that the compounds include numerous other valuable species as shown by the previously mentioned U.S. patent. It will be further understood that, while individual salts, and in some cases, enantiomers, are mentioned below and are of particular interest, other salts, and enantiomers, diastereomers, and racemates, are likewise valuable and are included in formula I as agents for the present invention.

1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, maleate salt;  
 cis-1-(4-indolyloxy)-3-(4-phenylcyclohexyl-amino)-2-propanol, oxalate salt;  
 1-(4-indolyloxy)-3-(2-phenylethylamino)-2-propanol, oxalate salt;  
 1-(4-indolyloxy)-3-(3-phenylpropylamino)-2-propanol, oxalate salt;  
 1-(4-indolyloxy)-3-(4-phenylbutylamino)-2-propanol, oxalate salt;  
 1-(4-indolyloxy)-3-cyclopentylamino-2-propanol, maleate salt;  
 1-(4-indolyloxy)-3-cycloheptylamino-2-propanol; (S)-(-)-1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, maleate salt;  
 (+)-1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, maleate salt;  
 1-(4-indolyloxy)-3-(3-methylcyclohexylamino)-2-propanol;  
 1-(4-indolyloxy)-3-(4-methylcyclohexylamino)-2-propanol;  
 1-(4-indolyloxy)-3-(5-phenylpentylaminol)-2-propanol, oxalate salt;  
 1-(4-indolyloxy)-3-(6-phenylhexylamino)-2-propanol, oxalate salt;  
 1-(4-indolyloxy)-3-(2,3-dimethylcyclohexyl-amino)-2-propanol, oxalate salt;  
 (+)-1-(4-indolyloxy)-3-(3-pentylamino)-2-propanol;  
 (R)-(+)-1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, butanedioate salt;  
 (R)-(-)-1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, butanedioate salt;  
 1-(2-trifluoromethyl-4-benzimidazolyl)-3-(4-phenylbutylamino)-2-propanol;  
 (exo)-1-(4-indolyloxy)-3-(norbornylamino)-2-propanol;  
 (endo)-1-(4-indolyloxy)-3-(norbornylamino)-2-propanol;  
 1-(1-naphthalenyloxy)-3-cycloheptylamino-2-propanol, oxalate salt;  
 1-(2-cyclopentylphenoxy)-3-cycloheptylamino-2-propanol, oxalate salt;  
 1-(2-cyclohexylphenoxy)-3-cyclooctylamino-2-propanol, oxalate salt;  
 1-(2-cycloheptylphenoxy)-3-(1,2,3-trimethyl-2-propylamino)-2-propanol, oxalate salt; and

1-(2-cyclopropylphenoxy)-3-(1,1-dimethylbutyl-amino)-2-propanol, oxalate salt.

The group of the compounds of formula I wherein the group Ar is indolyl or substituted indolyl constitutes a further preferred class of 5-HT<sub>1A</sub> antagonists; and the compounds of formula 1 wherein Z is (C<sub>4</sub>-C<sub>8</sub> cycloalkyl) optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl; or Z represents optionally phenyl substituted C<sub>2</sub>-C<sub>10</sub> alkyl where the phenyl group can be optionally substituted with R<sub>2</sub>; constitute further particularly preferred classes of compounds for use in the present invention.

All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

While all combinations of first component and second component compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

citalopram/pindolol  
 fluvoxamine/penbutolol  
 paroxetine/penbutolol  
 citalopram/propranolol

fluvoxamine/propranolol  
 paroxetine/propranolol  
 paroxetine/tertatolol  
 fluvoxamine/tertatolol  
 5 citalopram/tertatolol  
 citalopram/4-(2-hydroxy-3-cyclohexylaminopropoxy)indole  
 fluvoxamine/4-(2-hydroxy-3-cyclohexylaminopropoxy)indole  
 paroxetine/4-(2-hydroxy-3-cyclohexylaminopropoxy)indole

10 It will be understood by the skilled reader that all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

#### 15 Administration

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials,
 20 and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

25 Citalopram: from about 5 to about 50 mg once/day; preferred, from about 10 to about 30 mg once/day;  
 Fluvoxamine: from about 20 to about 500 mg once/day; preferred, from about 50 to about 300 mg once/day;  
 Paroxetine: from about 5 to about 100 mg once/day; preferred, from about 50 to about 300 mg once/day.  
 Pindolol: from about 1 to about 60 mg once-thrice/day; preferred, from about 5 to about 60 mg once-thrice/day;  
 also preferred, from about 1 to about 10 mg twice/day;  
 30 Penbutolol: from about 2 to about 80 mg once/day; preferred, from about 10 to about 80 mg once/day; also preferred, from about 2 to about 20 mg once/day;  
 Propranolol: from about 10 to about 240 mg once-twice/day; preferred, from about 10 to about 120 mg twice/day;  
 also preferred, from about 40 to about 240 mg once-twice/day;  
 4-(2-Hydroxy-3-cyclohexylaminopropoxy)indole: from about 1 to about 50 mg once-twice/day; preferred, from  
 35 about 1 to about 10 mg twice/day.

In more general terms, one would create a combination of the present invention by choosing a dosage of first component compound according to the spirit of the above guideline, and choosing a dosage of the second component compound in the general range of from about 1 to about 250 mg/dose. More preferred dosages, depending on the
 40 compound, would be from about 1 to about 100 mg/dose, and even more preferred dosages would be likely to be found in the range of from about 1 to about 50 mg/dose, ideally from about 1 to about 25 mg/dose.

The adjunctive therapy of the present invention is carried out by administering a first component together with one of the second component compounds in any manner which provides effective levels of the two compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so
 45 oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the other may be administered by the trans-dermal, per-
 50 cutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

It is particularly preferred, however, for the adjunctive combination to be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both a first component and a second component compound are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive
 55 pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of

both compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compound. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compound. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

The second component compounds, taken as a class, have short lives in the body and, accordingly, provide only short periods of activity following each dose. For example, pindolol is routinely administered twice/day in the prior art, and it has been administered even more often. In the context of the present invention, it is therefore preferred to administer the second component compounds in a manner which supplies a substantially constant blood level of the second component in the body of the patient, at a sufficiently high level to provide a substantially constant degree of potentiation of the action of the first component.

When the invention is carried out in this manner, the provisos in the general definition in the Summary are not operative; for example, the combination of citalopram and (S)-UH-301 is included in the invention when this manner of administration is used.

It is not intended, of course, that the present invention or any method of human treatment can provide a truly constant blood level and degree of potentiation. Biological processes always vary and prevent precisely constant results. The term "substantially constant" is used herein to refer to administration resulting in blood levels and degrees of potentiation which are sufficiently constant as to provide continuous improved efficacy over a treatment day, compared to the efficacy of the first component compound alone. Another way to consider substantially constant potentiation is by comparing the availability of serotonin, norepinephrine and dopamine in the brain of the patient. By "substantially constant" in such terms is meant a condition where the peak and the valley of availability differ by no more than about a factor of 2 over the course of a treatment day. Another way to consider "substantially constant" is a condition where the peak and valley differ by no more than about a factor of 1.5; or they differ by no more than a range of from about 1.5 to about 3.

Such administration of the second component may be provided by means known to pharmaceutical scientists. For example, the total daily dosage of a second component may be formulated in a manner which provides a substantially constant flow of compound to the patient. To consider only pindolol, at least the following references teach sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945, buccal tape; German Patent 2732335, tablets; U.S. Patent 5260066, cryogels; European Patent Publication 361894, liposomes; Japanese Patent 84-66710, transdermal patches. Pharmaceutical scientists are acquainted in modern practice with the manners of adjusting a sustained release formulation to provide the desired rate of administration of a given compound and such formulations can be prepared by the skill of the pharmaceutical art of the compounds used as second components here.

Such formulations of a second component compound may be combined in a single dosage form with the chosen first component compound. For example, a small tablet or pellets of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule, with the first component compound. Alternatively, a transdermal patch may be prepared which has a relatively rapidly releasing area of first component, and a relatively slowly releasing area of second component. Still further, a suspension may be prepared in which the first component is present as particles of pure compound, and the particles of the second component are coated to provide sustained release in the body. In such manners, the availability of the second component may be adjusted to provide the desired substantially constant blood levels and, hence, substantially constant potentiation of the first component. Compositions so adapted for providing substantially constant potentiation of the first component are preferred compositions of the present invention.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the first component and the second component compound. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algin and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

Tablets are often coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

#### Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

|                           | Quantity (mg/capsule) |
|---------------------------|-----------------------|
| Citalopram, hydrochloride | 20 mg                 |
| Pindolol                  | 30                    |
| Starch, dried             | 200                   |
| Magnesium stearate        | 10                    |
| Total                     | 260 mg                |

#### Formulation 2

A tablet is prepared using the ingredients below:

|                             | Quantity (mg/capsule) |
|-----------------------------|-----------------------|
| Fluvoxamine, hydrochloride  | 10                    |
| (-)-Penbutolol              | 40                    |
| Cellulose, microcrystalline | 400                   |

# EP 0 714 663 A2

(continued)

|                        | Quantity (mg/capsule) |
|------------------------|-----------------------|
| Silicon dioxide, fumed | 10                    |
| Stearic acid           | 5                     |
| Total                  | 465 mg                |

The components are blended and compressed to form tablets each weighing 465 mg.

## Formulation 3

An aerosol solution is prepared containing the following components:

|                                       | Weight |
|---------------------------------------|--------|
| Paroxetine, hydrochloride             | 10     |
| (S)-UH-301                            | 10     |
| Ethanol                               | 25.75  |
| Propellant 22 (Chlorodifluoromethane) | 70.00  |
| Total                                 | 115.75 |

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

## Formulation 4

Tablets, each containing 80 mg of active ingredient, are made as follows:

|   |        |
|---|--------|
| Fluvoxamine, hydrochloride                      | 20 mg  |
| (-)-Penbutolol                                  | 60 mg  |
| Starch  | 45 mg  |
| Microcrystalline cellulose                      | 35 mg  |
| Polyvinylpyrrolidone (as 10% solution in water) | 4 mg   |
| Sodium carboxymethyl starch                     | 4.5 mg |
| Magnesium stearate                              | 0.5 mg |
| Talc  | 1 mg   |
| Total   | 170 mg |

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinyl- pyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

## Formulation 5

Capsules, each containing 130 mg of active ingredient, are made as follows:

|                            |        |
|----------------------------|--------|
| Paroxetine, hydrochloride  | 30 mg  |
| Propranolol                | 100 mg |
| Starch                     | 59 mg  |
| Microcrystalline cellulose | 59 mg  |

## EP 0 714 663 A2

(continued)

|                    |        |
|--------------------|--------|
| Magnesium stearate | 2 mg   |
| Total              | 250 mg |

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U. S. sieve, and filled into hard gelatin capsules in 250 mg quantities.

### Formulation 6

Suppositories, each containing 45 mg of active ingredient, are made as follows:

|                                 |          |
|---------------------------------|----------|
| Citalopram, hydrochloride       | 5 mg     |
| Propanolol                      | 40 mg    |
| Saturated fatty acid glycerides | 2,000 mg |
| Total                           | 2,045 mg |

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

### Formulation 7

Suspensions, each containing 70 mg of active ingredient per 5 ml dose, are made as follows:

|                                     |         |
|-------------------------------------|---------|
| Fluvoxamine, racemic, hydrochloride | 10 mg   |
| Propanolol                          | 60 mg   |
| Sodium carboxymethyl cellulose      | 50 mg   |
| Syrup                               | 1.25 ml |
| Benzoic acid solution               | 0.10 ml |
| Flavor                              | q.v.    |
| Color                               | q.v.    |
| Purified water to total             | 5 ml    |

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

### Formulation 8

An intravenous formulation may be prepared as follows:

|                           |          |
|---------------------------|----------|
| Citalopram, hydrochloride | 10 mg    |
| Propanolol                | 20 mg    |
| Isotonic saline           | 1,000 ml |

### Benefit of the Invention

As stated above, the benefit of the invention is its ability to augment the increase in availability of serotonin, norepinephrine and dopamine caused by the first component compounds, resulting in improved activity in treating the various conditions described below in detail. The increase in availability of serotonin is particularly important and is a preferred aspect of the invention. Further, the invention provides a more rapid onset of action than is usually provided by treatment with the first component alone.

Preferred pathological conditions to be treated by the present method of adjunctive therapy include depression, obsessive-compulsive disease and obesity.

Depression in its many variations has recently become much more visible to the general public than it has previously been. It is now recognized as an extremely damaging disorder, and one that afflicts a surprisingly large fraction of the population. Suicide is the most extreme symptom of depression, but millions of people, not quite so drastically afflicted, live in misery and partial or complete uselessness, and afflict their families as well by their affliction. The introduction of fluoxetine was a breakthrough in the treatment of depression, and depressives are now much more likely to be diagnosed and treated than they were only a decade ago. The three first component compounds herein are in use for the treatment of depression.

Depression is often associated with other diseases and conditions, or caused by such other conditions. For example, it is associated with Parkinson's disease; with HIV; with Alzheimer's disease; and with abuse of anabolic steroids. Depression may also be associated with abuse of any substance, or may be associated with behavioral problems resulting from or occurring in combination with head injuries, mental retardation or stroke. Depression in all its variations is a preferred target of treatment with the present adjunctive therapy method and compositions.

Obsessive-compulsive disease appears in a great variety of degrees and symptoms, generally linked by the patient's uncontrollable urge to perform needless, ritualistic acts. Acts of acquiring, ordering, cleansing and the like, beyond any rational need or rationale, are the outward characteristic of the disease. A badly afflicted patient may be unable to do anything but carry out the rituals required by the disease.

Obesity is common in the populations of industrial and developing countries. It has been found that serotonin reuptake inhibitors will enable an obese patient to lose weight, with the resulting benefit to the patient's circulation and heart condition, as well as general well being and energy.

Urinary incontinence is classified generally as stress or urge incontinence, depending on whether its root cause is the inability of the sphincter muscles to keep control, or the overactivity of the bladder muscles.

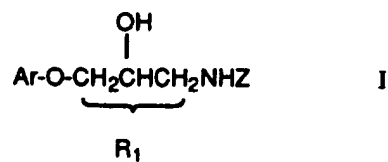
The present invention is useful for treating many other diseases, disorders and conditions as well, as set out below. In many cases, the diseases to be mentioned here are classified in the International Classification of Diseases, 9th Edition (ICD), or in the Diagnostic and Statistical Manual of Mental Disorders, 3rd Version Revised, published by the American Psychiatric Association (DSM). In such cases, the ICD or DSM code numbers are supplied below for the convenience of the reader.

depression, ICD 296.2 & 296.3, DSM 296, 294.80, 293.81, 293.82, 293.83, 310.10, 318.00, 317.00 migraine  
pain, particularly neuropathic pain  
bulimia, ICD 307.51, DSM 307.51  
premenstrual syndrome or late luteal phase syndrome, DSM 307.90  
alcoholism, ICD 305.0, DSM 305.00 & 303.90  
tobacco abuse, ICD 305.1, DSM 305.10 & 292.00  
panic disorder, ICD 300.01, DSM 300.01 & 300.21  
anxiety, ICD 300.02, DSM 300.00  
post-traumatic syndrome, DSM 309.89  
memory loss, DSM 294.00  
dementia of aging, ICD 290  
social phobia, ICD 300.23, DSM 300.23  
attention deficit hyperactivity disorder, ICD 314.0  
disruptive behavior disorders, ICD 312  
impulse control disorders, ICD 312, DSM 312.39 & 312.34  
borderline personality disorder, ICD 301.83, DSM 301.83  
chronic fatigue syndrome  
premature ejaculation, DSM 302.75  
erectile difficulty, DSM 302.72  
anorexia nervosa, ICD 307.1, DSM 307.10  
disorders of sleep, ICD 307.4  
autism  
mutism  
trichotillomania

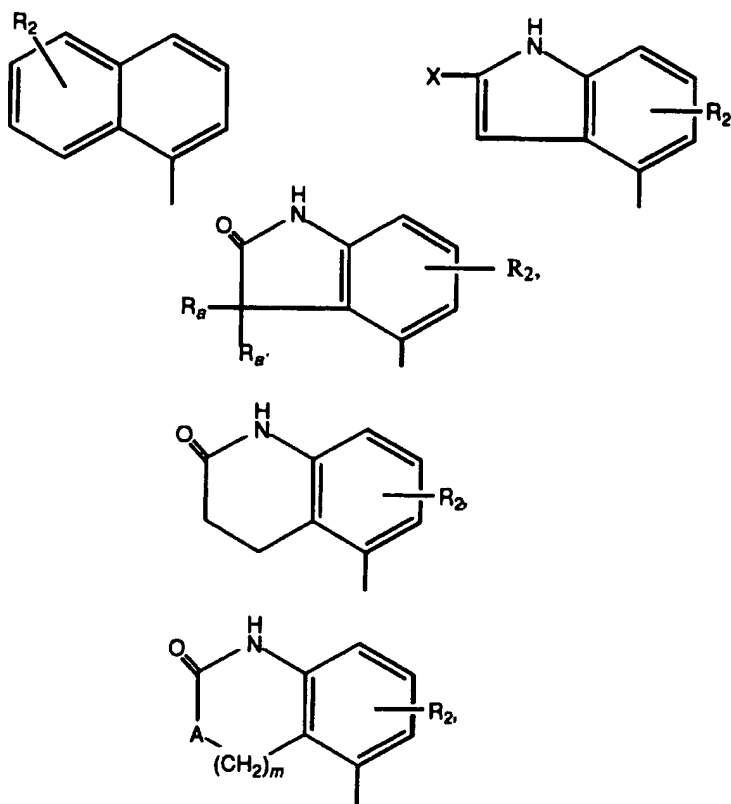
## Claims

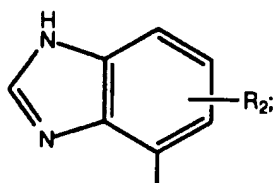
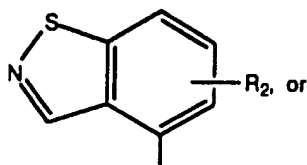
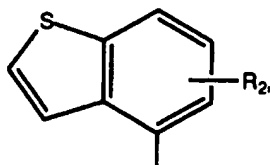
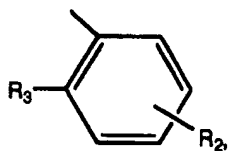
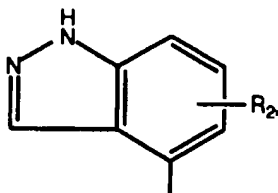
1. Use for the manufacture of a medicament for potentiating the action of a first component chosen from the group consisting of citalopram, fluvoxamine and paroxetine in increasing the availability of serotonin, norepinephrine and dopamine in the brain, of a combination of a first component and a second component chosen from the group

consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula

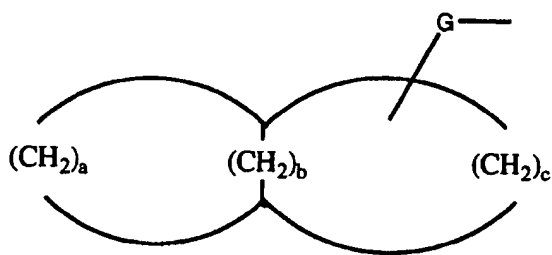


wherein Ar is

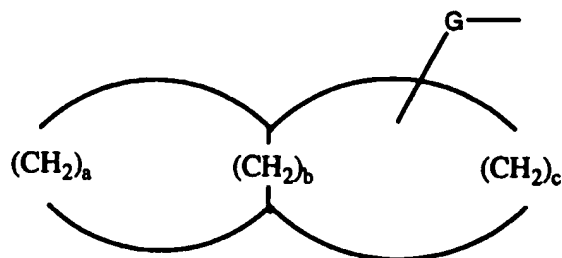




$R_1$  is an optional methyl group substituted on one of the three connecting carbon atoms;  
 $R_2$  is hydrogen,  $C_1$ - $C_4$  alkyl, trifluoromethyl, hydroxy,  $(C_1$ - $C_4$  alkyl)-O-,  $(C_1$ - $C_4$  alkyl)-S(O) $_p$ -, or halo;  
 $R_3$  is  $C_3$ - $C_8$  cycloalkyl or a bicycloalkyl group of the formula



where  $a$  and  $c$  are independently 1-5,  $b$  is 0-5, and  $(a+c)$  is greater than 2;  
 $Z$  is a straight or branched  $C_4$ - $C_{10}$  alkane, alkene, or alkyne group;  $(C_4$ - $C_8$  cycloalkyl) optionally substituted with  $C_1$ - $C_4$  alkyl or phenyl; a bicycloalkyl group of the formula



wherein a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2; optionally phenyl substituted C<sub>2</sub>-C<sub>10</sub> alkyl where the phenyl group can be optionally substituted with R<sub>2</sub> as previously defined; or (C<sub>1</sub>-C<sub>4</sub> alkylidene)-T-(C<sub>1</sub>-C<sub>4</sub> alkyl), where T is -O-, -S-, -SO-, or -SO<sub>2</sub>-;

where

each G is independently a bond or C<sub>1</sub>-C<sub>4</sub> alkylidene;

X is -H, -COY, -CN, or C<sub>1</sub>-C<sub>4</sub> alkyl;

Y is -OH, -O-(C<sub>1</sub>-C<sub>4</sub> alkyl), or -NH<sub>2</sub>;

R<sub>a</sub> and R<sub>a</sub>' are independently hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl, or when taken together with the carbon atom to which they are attached form a C<sub>3</sub>-C<sub>8</sub> cycloalkyl ring;

p is 0, 1, or 2;

A is -O-, -S-, -NH-, or -NCH<sub>3</sub>-; and

m is 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof;

provided that when the first component is citalopram, the second component is not (S)-UH-301 or penbutolol, and when the first component is paroxetine or fluvoxamine, the second component is not pindolol.

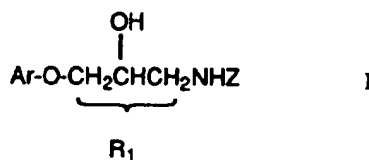
2. A use of claim 1 wherein the first component is citalopram.

3. A use of claim 1 wherein the first component is fluvoxamine.

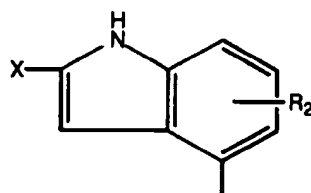
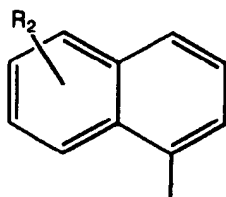
4. A use of claim 1 wherein the first component is paroxetine.

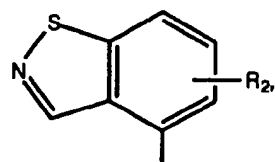
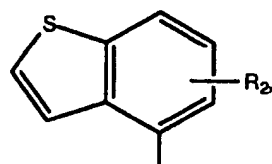
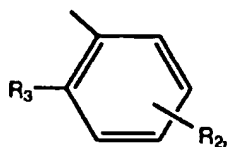
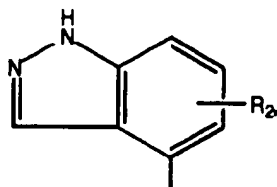
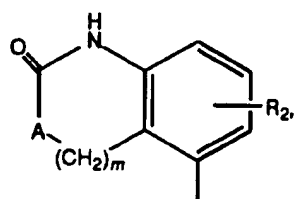
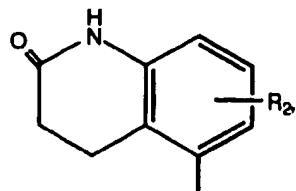
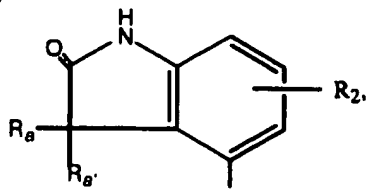
5. A use of any one of claims 1-4 wherein the second component is chosen from the group consisting of pindolol, penbutolol, propranolol, tertatolol, and 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.

6. Use for the manufacture of a medicament for treating a pathological condition which is created by or is dependent upon decreased availability of serotonin, norepinephrine or dopamine, of a first component chosen from the group consisting of citalopram, fluvoxamine and paroxetine, in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula



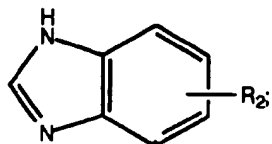
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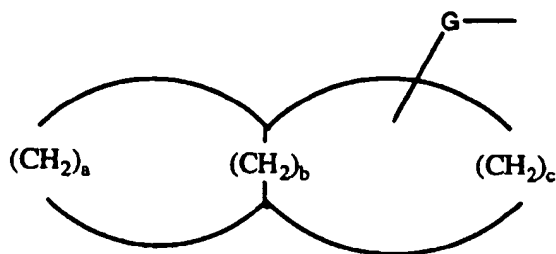
or



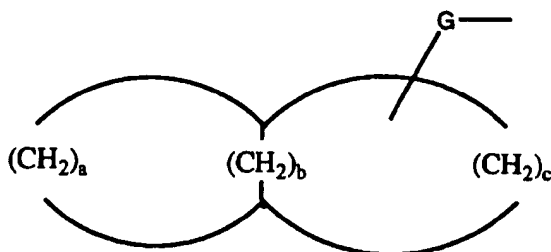
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$R_1$  is an optional methyl group substituted on one of the three connecting carbon atoms;  
 $R_2$  is hydrogen,  $C_1$ - $C_4$  alkyl, trifluoromethyl, hydroxy,  $(C_1$ - $C_4$  alkyl)-O-,  $(C_1$ - $C_4$  alkyl)-S(O) $_p$ -, or halo;  
 $R_3$  is  $C_3$ - $C_8$  cycloalkyl or a bicycloalkyl group of the formula



where a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2;  
Z is a straight or branched  $C_4$ - $C_{10}$  alkane, alkene, or alkyne group; ( $C_4$ - $C_8$  cycloalkyl) optionally substituted with  $C_1$ - $C_4$  alkyl or phenyl; a bicycloalkyl group of the formula



wherein a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2; optionally phenyl substituted  $C_2$ - $C_{10}$  alkyl where the phenyl group can be optionally substituted with R<sub>2</sub> as previously defined; or ( $C_1$ - $C_4$  alkylidene)-T-( $C_1$ - $C_4$  alkyl), where T is -O-, -S-, -SO-, or -SO<sub>2</sub>-;

where

each G is independently a bond or  $C_1$ - $C_4$  alkylidene;

X is -H, -COY, -CN, or  $C_1$ - $C_4$  alkyl;

Y is -OH, -O-( $C_1$ - $C_4$  alkyl), or -NH<sub>2</sub>;

R<sub>a</sub> and R<sub>a</sub>' are independently hydrogen or  $C_1$ - $C_3$  alkyl, or when taken together with the carbon atom to which they are attached form a  $C_3$ - $C_8$  cycloalkyl ring;

p is 0, 1, or 2;

A is -O-, -S-, -NH-, or -NCH<sub>3</sub>-; and

m is 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof;

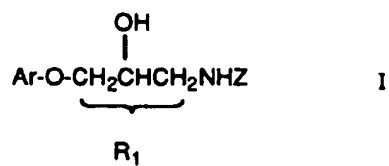
provided that when the first component is citalopram, the second component is not (S)-UH-301 or penbutolol; and when the first component is fluvoxamine or paroxetine, the second component is not pindolol.

7. A use of claim 6 wherein the pathological condition is depression.

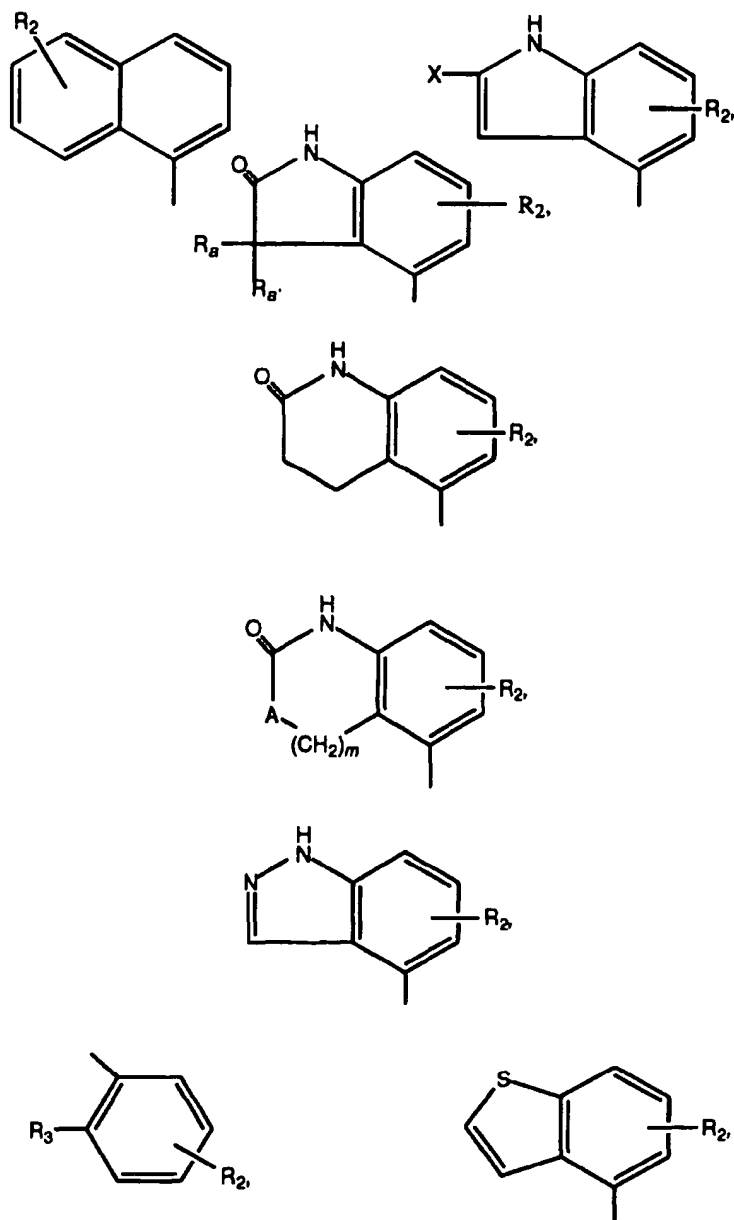
8. A use of claim 6 wherein the pathological condition is obsessive compulsive disease.

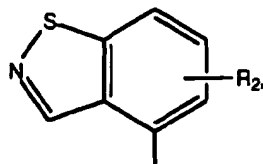
9. A use of any one of claims 6-8 wherein the second component is chosen from the group consisting of pindolol, penbutolol, propranolol, tertatolol, and 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.

10. A pharmaceutical composition which comprises a first component chosen from the group consisting of citalopram, fluvoxamine and paroxetine in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula

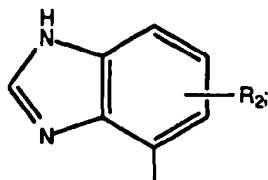


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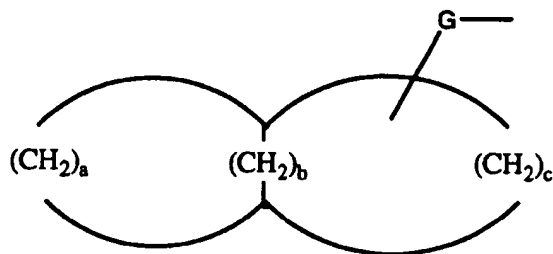




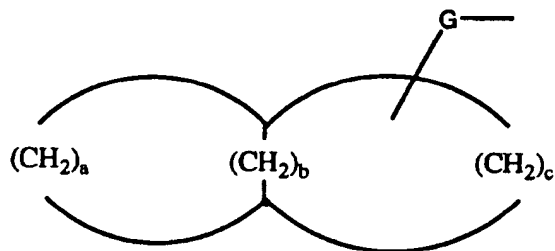
or



$R_1$  is an optional methyl group substituted on one of the three connecting carbon atoms;  
 $R_2$  is hydrogen,  $C_1$ - $C_4$  alkyl, trifluoromethyl, hydroxy,  $(C_1$ - $C_4$  alkyl)-O-,  $(C_1$ - $C_4$  alkyl)-S(O)<sub>p</sub>-, or halo;  
 $R_3$  is  $C_3$ - $C_8$  cycloalkyl or a bicycloalkyl group of the formula



where  $a$  and  $c$  are independently 1-5,  $b$  is 0-5, and  $(a+c)$  is greater than 2;  
 $Z$  is a straight or branched  $C_4$ - $C_{10}$  alkane, alkene, or alkyne group;  $(C_4$ - $C_8$  cycloalkyl) optionally substituted with  $C_1$ - $C_4$  alkyl or phenyl; a bicycloalkyl group of the formula



wherein  $a$  and  $c$  are independently 1-5,  $b$  is 0-5, and  $(a+c)$  is greater than 2; optionally phenyl substituted  $C_2$ - $C_{10}$  alkyl where the phenyl group can be optionally substituted with  $R_2$  as previously defined; or  $(C_1$ - $C_4$  alkylidene)-T-( $C_1$ - $C_4$  alkyl), where T is -O-, -S-, -SO-, or -SO<sub>2</sub>-;

where

each G is independently a bond or  $C_1$ - $C_4$  alkylidene;

X is -H, -COY, -CN, or  $C_1$ - $C_4$  alkyl;

Y is -OH, -O-( $C_1$ - $C_4$  alkyl), or -NH<sub>2</sub>;

$R_a$  and  $R_a'$  are independently hydrogen or  $C_1$ - $C_3$  alkyl, or when taken together with the carbon atom to which they are attached form a  $C_3$ - $C_8$  cycloalkyl ring;

$p$  is 0, 1, or 2;

A is -O-, -S-, -NH-, or -NCH<sub>3</sub>-; and

$m$  is 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof;

provided that when the first component is citalopram, the second component is not (S)-UH-301 or penbutolol;  
and when the first component is fluvoxamine or paroxetine, the second component is not pindolol.

11. A composition of claim 10 wherein the second component is chosen from the group consisting of pindolol, penbutolol, propranolol, tertatolol and 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.

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(71) Applicant: **ELI LILLY AND COMPANY**  
Indianapolis, Indiana 46285 (US)

(72) Inventors:  
• **Oguiza, Juan Ignacio**  
28700 San Sebastian de los Reyes Madrid (ES)

• **Wong, David Taiwai**  
Indianapolis, Indiana 46226 (US)

(74) Representative: **Tapping, Kenneth George et al**  
**Lilly Industries Limited**  
**European Patent Operations**  
**ErI Wood Manor**  
**Windlesham Surrey GU20 6PH (GB)**

(54) **Potentialiation of drug response by a serotonin 1A receptor antagonist**

(57) The power of citalopram, fluvoxamine and paroxetine to increase the availability of serotonin, nore-

pinephrine and dopamine, particularly serotonin, is augmented by administration in combination with a drug which is a serotonin 1A receptor antagonist.



European Patent  
Office

# PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 95 30 8407  
shall be considered, for the purposes of subsequent  
proceedings, as the European search report

| DOCUMENTS CONSIDERED TO BE RELEVANT  |  |   |  |
|--|--|---|--|
| Category   | Citation of document with indication, where appropriate, of relevant passages  | Relevant to claim   | CLASSIFICATION OF THE APPLICATION (Int.Cl.6)   |
| X  | EUROPEAN JOURNAL OF PHARMACOLOGY,<br>vol. 260, 1994,<br>pages 251-255, XP000605645<br>HJORTH, AUERBACH: "FURTHER EVIDENCE FOR<br>THE IMPORTANCE OF 5-HT1A AUTORECEPTORS IN<br>THE ACTION OF SELECTIVE SEROTONIN REUPTAKE<br>INHIBITORS"<br>* page 252-254, left-hand column *  | 1,2,4-7,<br>9-11  | A61K45/06<br>A61K31/445<br>//(A61K31/445,<br>31:135),<br>(A61K31/445,<br>31:145),<br>(A61K31/445,<br>31:34),<br>(A61K31/445,<br>31:40) |
| X  | PROCEEDINGS OF THE 6TH INTERNATIONAL<br>CONFERENCE ON IN VIVO METHODS,<br>17 - 20 September 1994,<br>pages 209-210, XP000607002<br>BEL ET AL: "NEUROBIOLOGICAL BASIS FOR THE<br>POTENTIATION OF THE ANTIDEPRESSANT EFFECT<br>OF 5-HT UPTAKE INHIBITORS BY THE 5-HT1A<br>ANTAGONIST PINDOLOL"<br>* the whole document * | 1-7,9-11  |  |
|  |  |   | TECHNICAL FIELDS<br>SEARCHED (Int.Cl.6)  |
|  |  |   | A61K   |
| INCOMPLETE SEARCH  |  |   |  |
| <p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely:</p> <p>Claims searched incompletely:</p> <p>Claims not searched:</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p> |  |   |  |
| Place of search  |  | Date of completion of the search  | Examiner   |
| THE HAGUE  |  | 6 November 1996   | Kanbier, D   |
| CATEGORY OF CITED DOCUMENTS  |  |   |  |
| <p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>D : non-written disclosure</p> <p>P : intermediate document</p>   |  | <p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>&amp; : member of the same patent family, corresponding document</p> |  |

EPO FORM 1503 03.82 (P04 D07)



European Patent Office

EP 95 30 8407 - C -

**INCOMPLETE SEARCH**

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search in the state of the art on the basis of some of the claims.

Claims searched completely:

Claims searched incompletely: 1,6,10

Claims not searched:

Reason for the limitation of the search: In view of the large number of compounds, which are defined by the general formula/description, used in claims 1,6,10, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see Guidelines, part B, chapter III, paragraph 3.6).



European Patent  
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## PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 95 30 8407

| DOCUMENTS CONSIDERED TO BE RELEVANT |  |                   | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
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| Category                            | Citation of document with indication, where appropriate, of relevant passages  | Relevant to claim |  |
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| A                                   | * page 40 *  | 6,9               |  |
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| A                                   | JOURNAL OF NEUROCHEMISTRY,<br>vol. 60, no. 2, 1993,<br>pages 776-779, XP000604419<br>HJORTH: "SEROTONIN 5-HT1A AUTORECEPTOR<br>BLOCKADE POTENTIATES THE ABILITY OF THE<br>5-HT REUPTAKE INHIBITOR CITALOPRAM ..."<br>* page 777-779, left-hand column *                  | 1,2,5-7,<br>9-11  |  |
|                                     |  |                   |  |

EPO FORM 150 (11/82) (P4/C10)

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